Mathematical analysis of microRNA regulation reveals crosstalk limits and increased noise in gene expression

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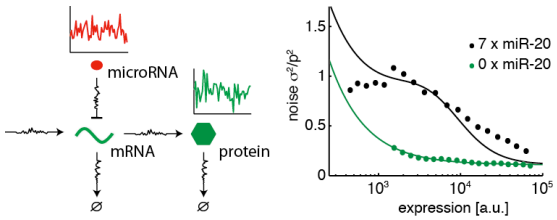
Short Abstract — **microRNAs may regulate hundreds of genes, but they only weakly repress their expression and the functional significance of this 'fine-tuning' - despite binding site conservation - is unclear. To test whether this selection is due to microRNAs reducing gene expression noise, or mediating mRNA-crosstalk through sequestration, we built a simple mathematical model and validated predictions using single cell experimental data. In disagreement with some reports, our results show microRNA regulation significantly *increases* noise in regulated genes and the reported amount of microRNA-mediated crosstalk is not consistent with our predicted upper limits for this effect. We conclude that microRNA noise and crosstalk correlate the expression of co-regulated genes.**

Keywords **— microRNA regulation, noise, crosstalk, mathematical model, single cell data**

I. Introduction

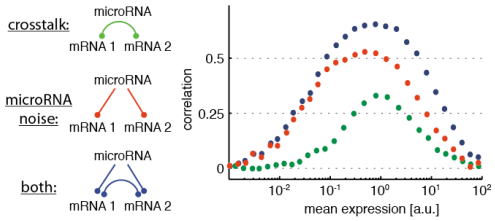
MicroRNAs are thought target hundreds of genes[1], but their repressive effects are mostly small [2]. Possible functional significance of fine-tuning gene regulation could be dampening transcriptional noise[3], or conferring robustness to certain cellular processes, as microRNAs are often found to target functionally related genes[4]. Recently it was also proposed that microRNA regulation facilitates gene-to-gene communication through crosstalk[5].

II. Results



We use a comprehensive mathematical model and the re-analysis of published single cell data[6] to show that microRNA regulation significantly increases noise. Our model predicts that the up to four-fold noise increase in the expression of miR-20 regulated reporter constructs can only be explained by extrinsic microRNA noise, propagated through the microRNA regulation.

Based on our model analysis and large-scale simulations we identify requirements for microRNA mediated crosstalk between co-regulated genes and find a strong quantitative upper limit for the strength of crosstalk. This upper limit is in disagreement with recently observed crosstalk between the tumor suppressor gene PTEN and other co-regulated genes in various cancer cell lines[5,7,8].



Finally, we bring together our findings on extrinsic microRNA noise and crosstalk to show that microRNA regulation correlates the expression of co-regulated genes.

III. Conclusion

Our results suggest that microRNA can confer robustness to cellular processes by co-regulating involved genes. Also, exploiting increased noise levels, microRNAs might function in certain processes where heterogeneous response of a tissue might be advantageous.

The finding that the upper limit of crosstalk identified in our model is in disagreement with published data on PTEN crosstalk suggests that there might be so far unknown feedback loops amplifying crosstalk-induced PTEN changes.

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